Clinical studies with high flow nasal cannula oxygen delivery in 2015

David Sotello MD, Hawa Edriss MD, Kenneth Nugent MD

We identified 21 clinical studies, including six in Respiratory Care, using high flow nasal cannula oxygenation (HFNC) published between January 1, 2015, and January 31, 2016. Seven clinical studies were randomized controlled trials with patients in either intensive care units or emergency departments (Table 1). Frat and coworkers reported a multicentered randomized controlled trial involving 310 patients with hypoxic acute respiratory failure and a ratio of PaO$_2$/FiO$_2$ of 300 or less. These patients were randomized to either HFNC with a flow rate of 50 L per minute and a FiO$_2$ of 1.0, or nonrebreathing masks with a rate of 10 L per minute or more, or noninvasive ventilation (NIV) with adjustment of the FiO$_2$ to maintain an oxygenation goal of 92% saturation or more. There were no differences in the time between the intervention to intubation and in the intubation rates in these three groups (primary outcome), but patients with a PaO$_2$/FiO$_2$ less than 200 had a decreased rate of intubation (post hoc analysis). The crude ICU mortality was lower in the HFNC group. The 90 day mortality rates were lower in patients in the HFNC group who did not require intubation. However, there were no differences in mortality in patients who required intubation. This study reported that ventilator-free days were higher in the HFNC group (24±8) compared to the nonrebreather study arm (22±10) and the NIV study arm (19±12). The authors concluded that the lower mortality rate noted with HFNC might have resulted from the reduced intubation rate in this group, especially in those with more severe respiratory failure and a PaO$_2$/FiO$_2$ ratio of less than 200. It was observed that patients who were treated with HFNC had more comfort, less dyspnea, and lower respiratory rates, and this was attributed to the possible effects of heat, humidification, and the level of PEEP created by the high flow rate of the inspired gas.

Lemiale et al reported that HFNC oxygenation did not reduce the need for mechanical ventilation or improve patient comfort when compared to Venturi masks in immunocompromised patients with acute hypoxemic respiratory failure. A noninferiority study conducted by Stephan and his colleagues between 2011 and 2014 compared HFNC and BiPAP using full facemasks in post cardiothoracic surgery patients who had acute respiratory failure, including failed spontaneous breathing trials and failed extubation following the surgery, or were at risk for acute respiratory failure. This study included 830 patients randomized to either HFNC with an initial flow rate at 50 L per minute and FiO$_2$ fraction of 0.5 or BiPAP started at pressure support of 8 cm H$_2$O to achieve a tidal volume of 8 ml/kg and respiratory rate of less than 25 breaths per minute for at least four hours per day with adjustments to keep SaO$_2$ at 92-98%. The rate of intubation was 21.0% (HFNC) and 21.9% (BiPAP). They found that HFNC support was not inferior to the use of BiPAP in these patients and concluded that the results support the use of HFNC in similar post-operative patients. Oxygenation was better with BiPAP (higher PaO$_2$/FiO$_2$ values) and that was thought due to higher positive end expiratory pressure. HFNC was associated with lower PaCO$_2$ possibly due to higher inspiratory flows and tidal volumes. The study reported no difference in the degree of discomfort or dyspnea.
### Table 1. Randomized trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>#</th>
<th>Type of pts</th>
<th>Location</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frat1</td>
<td>Multicenter, open-label, RCT</td>
<td>310</td>
<td>Hypoxemic ARF</td>
<td>ICU</td>
<td>HFNC started at 50 L/min $\text{FiO}_2$ 1.0 then adjusted to keep $O_2$ Sat $\geq 92$.</td>
<td>Nonrebreather mask or NIV to keep $O_2$ Sat $\geq 92%$.</td>
<td>No difference in intubation rates. Lower 90 day mortality in HFNC.</td>
</tr>
<tr>
<td>Lemiale2</td>
<td>Multi-center, parallel-group, RCT</td>
<td>100</td>
<td>Immuno-compromised patients with hypoxemic ARF</td>
<td>ICU</td>
<td>HFNC with initial flow was 40–50 L/min with an $\text{FiO}_2$ of 100%, then adjusted to maintain $\text{SpO}_2 \geq 95%$.</td>
<td>Venturi mask group with $\text{FiO}_2$ at 60% at 15L/min initially, adjusted to maintain $\text{SpO}_2 \geq 95%$.</td>
<td>HFNC did not reduce the need for mechanical ventilatory assistance or improve patient comfort compared to oxygen delivered by a Venturi mask.</td>
</tr>
<tr>
<td>Vourc’h3</td>
<td>Multi-center, open-labelled, RCT</td>
<td>124</td>
<td>Hypoxemic ARF requiring intubation, random allocation to HFNC or HFFM.</td>
<td>ICU</td>
<td>HFNC preoxygenation for 4 min with HFNC set at 60 l/min flow, $\text{FiO}_2$ 100%</td>
<td>In the control group (HFFM), preoxygenation was performed for 4 min with high $\text{FiO}_2$ facial mask (15 l/min oxygen flow)</td>
<td>Compared to HFFM, HFNC preoxygenation did not reduce the lowest level of saturation.</td>
</tr>
<tr>
<td>Stéphan4</td>
<td>Multicenter, non-inferiority trial, RCT</td>
<td>830</td>
<td>Post-cardiothoracic surgery ARF or at risk for ARF.</td>
<td>ICU</td>
<td>HFNC at 50 L/min, $\text{FiO}_2$ 50%, n = 414</td>
<td>BiPAP with a full-face mask for at least 4 hours per day (IPAP 8 cmH₂O, EPAP 4 cmH₂O, $\text{FiO}_2$ 50%), n = 416</td>
<td>High-flow nasal oxygen therapy was not inferior to BiPAP.</td>
</tr>
<tr>
<td>Rittayamai5</td>
<td>RCT</td>
<td>40</td>
<td>Acute dyspnea or hypoxemia</td>
<td>ED</td>
<td>HFNC at 35 L/min, $\text{FiO}_2$ adjusted to achieve a $\text{SpO}_2$ of $\geq 94%$ within the first 5 min and was continued for 60 min.</td>
<td>$O_2$ was supplied via a nasal cannula or non-rebreathing mask at a flow of 3–10 L/min to maintain an $\text{SpO}_2$ of $\geq 94%$ for 60 min.</td>
<td>HFNC significantly improved dyspnea and comfort compared with conventional oxygen therapy.</td>
</tr>
<tr>
<td>Bell6</td>
<td>RCT</td>
<td>100</td>
<td>Acute dyspnea</td>
<td>ED</td>
<td>HFNC</td>
<td>Standard $O_2$</td>
<td>Reduced RR (67% vs 39%), Lower % requiring an escalation in therapy (4.2% vs 19%)</td>
</tr>
<tr>
<td>Jones7</td>
<td>Pragmatic, open label RCT</td>
<td>303</td>
<td>Hypoxemic AFR</td>
<td>ED</td>
<td>HFNC at 40 L/min, $\text{FiO}_2$ 28%.</td>
<td>Standard $O_2$ with Venturi device, or nasal prongs using wall oxygen titrated with a flow meter(1–15 L/min).</td>
<td>Lower rate of intubation with HFNC (p=0.16). No difference in mortality or hospital LOS</td>
</tr>
</tbody>
</table>

ARF- acute respiratory failure, BiPAP- bilevel positive airway pressure, ED- emergency department, EPAP- expiratory airway pressure, HFNC- high flow nasal cannula oxygen, HFFM- high flow face mask, ICU- intensive care unit, IPAP- inspiratory positive airway pressure, LOS- length of stay, NIV- noninvasive ventilation, NA- not applicable, RCT-randomized controlled trial
Table 2 Retrospective studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>#</th>
<th>Type of pts</th>
<th>Location</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyun Cho⁸</td>
<td>Retrospective</td>
<td>75</td>
<td>Acute hypoxemic respiratory failure</td>
<td>ICU</td>
<td>Blended gases at 30-40 L/min and FiO₂ of 40-100% using a HFNC device. The primary therapeutic goal was SpO₂ &gt; 92% or PO₂ &gt; 65 mmHg.</td>
<td>N/A</td>
<td>37.3% intubated, 25.3% mortality. HFNC improved PaO₂, RR, HR, throughout the first 24 hours.</td>
</tr>
<tr>
<td>Nagata⁹</td>
<td>Retrospective</td>
<td>172</td>
<td>Hypoxemic respiratory failure</td>
<td>ICU Intermediate care unit Hospital</td>
<td>HFNC</td>
<td>Conventional oxygen therapy</td>
<td>No change in mortality, hospital LOS, mechanical ventilation (p&lt;0.01).</td>
</tr>
<tr>
<td>Sotello¹⁰</td>
<td>Retrospective</td>
<td>106</td>
<td>Respiratory failure</td>
<td>ICU Intermediate care unit Hospital</td>
<td>HFNC use, patients were subdivided into 2 subgroups: a step-up group (patients switched from standard O₂ to HFNC), and a step-down group (patients transitioned from NIV and/or mechanical ventilation to HFNC)</td>
<td>NA</td>
<td>PO₂ and O₂ saturations improved when patients were switched to HFNC in the step-up group. No significant difference between PO₂ and O₂ saturations in Step-down group.</td>
</tr>
<tr>
<td>Messi-ka¹¹</td>
<td>Prospective data, retrospective review</td>
<td>560</td>
<td>ARDS</td>
<td>ICU</td>
<td>HFNC</td>
<td></td>
<td>HFNC was used in 45 subjects with ARDS, only 40% required secondary intubation</td>
</tr>
<tr>
<td>Yoo¹²</td>
<td>Retrospective cohort</td>
<td>73</td>
<td>Post extubation respiratory failure</td>
<td>ICU</td>
<td>HFNC</td>
<td>NIV (historical cohort)</td>
<td>No difference in reintubation rate (79.4% vs 66.7%), ICU stay shorter in HFNC group</td>
</tr>
<tr>
<td>Roca¹³</td>
<td>Prospective data, retrospective review</td>
<td>37</td>
<td>Lung transplantation with ARF</td>
<td>ICU</td>
<td>HFNC</td>
<td>Conventional O₂</td>
<td>Relative risk for mechanical ventilation higher in O₂ group (1.5), NNT=3</td>
</tr>
<tr>
<td>Gaunt¹⁴</td>
<td>Retrospective</td>
<td>145</td>
<td>Hypoxemic ARF</td>
<td>ICU</td>
<td>Initial settings at 50 L/min and 50% FiO₂</td>
<td>Mechanical ventilation prior to HFNC</td>
<td>Intubation rate 20%, Reintubation 20% vs 20%, Mortality 14.5% vs. 11.4%. Early HFNC may be beneficial</td>
</tr>
</tbody>
</table>

ARDS- acute respiratory distress syndrome, ARF- acute respiratory failure, ED- emergency department, HFNC- high flow nasal cannula oxygen, HR- heart rate, ICU- intensive care unit, NA- not applicable, NIV- noninvasive ventilation, RR- respiratory rate
between the two groups. Vourc’h compared preoxy-
genation with either HFNC or high flow facemasks in
hypoxemic patients requiring intubation.3 There was
no difference in oxygenation status prior to intubation
in these two groups. Several studies have evaluated
the use of HFNC in emergency departments (ED).5,7
This method appears to significantly improve oxy-
genation and dyspnea when compared to conventional
oxygen therapy; it reduces respiratory rates and pos-
sibly the need for an escalation in therapeutic sup-
port. It does not appear to have a significant effect on
intubation rates, mortality, or hospital length of stay
in ED patients. These randomized trials suggest that
high flow nasal cannulas provide a good method for
oxygen delivery to patients with acute respiratory fail-
ure, acute respiratory distress in the ED, and in post-
operative patients. Outcomes were better in the Frat
study in patients with lower PaO$_2$/FiO$_2$ ratios.

Seven articles provided retrospective reviews of
HFNC use in hospitalized patients (Table 2).6-14 Most
of these patients were in intensive care units. Two
articles compared HFNC use with conventional oxy-
gen use; one compared it with noninvasive ventilation
based on a historical cohort.9,12,13 In general, oxygen
delivery with HFNC increased the PaO$_2$, reduced the
respiratory rate, and reduced heart rates. Most of the
studies found no important difference in outcomes,
but one study with 37 lung transplant patients who
required ICU readmission for acute respiratory failure
found that HFNC oxygen delivery reduced the risk for
mechanical ventilation (OR 0.43 [95% CI: 0.002-
0.88], P=0.04) when compared to conventional oxy-
genation.13 Additionally, patients treated with HFNC
who did not need mechanical ventilation had a high-
er survival. The relative risk for requiring mechanical
ventilation in the conventional oxygen therapy group
was 1.5 (1.02-2.21). The absolute risk reduction for
mechanical ventilation was 29.8% in the HFNC group,
and the number needed to treat to prevent one intu-
bation was three. Patients who failed HFNC treatment
had more infiltrates on chest x-ray and had more fre-
quent ARDS and shock during their ICU stays. Gaunt
et al suggested that early use of HFNC may be ben-
eficial in hypoxemic patients with acute respiratory fail-
ure to provide better support during the early phase
of treatment.14 Retrospective studies have important
limitations, but the results in lung transplantation pa-
patients are potentially important and need confirmation.

Four studies evaluated the physiological effects of
HFNC use, and three studies identified factors as-
associated with failure during HFNC use (Table 3).15-21
Jeong studied 973 patients with acute respiratory fail-
ure in an emergency department.15 These investiga-
tors demonstrated that HFNC use could decrease the
PaCO$_2$ in patients who presented to the emergency
department with PaCO$_2$ greater than 45 mmHg. Vargas
et al did relatively complex studies in 12 patients
with acute respiratory failure and measured esoph-
ageal pressures, breathing patterns, gas exchange,
and symptoms.18 High flow nasal cannula use was
compared to nonrebreathing masks and to CPAP.
High flow nasal cannula use reduced the inspiratory
effort and improved oxygenation when compared to
conventional O$_2$ therapy. However, patients on the
CPAP had bigger increases in PaO$_2$/FiO$_2$ ratios. Frat
demonstrated that HFNC use was better tolerated
than noninvasive ventilation in patients with acute res-
piratory failure in the medical intensive care units.17
However, PaO$_2$ increased more with noninvasive ven-
tilation. High flow nasal cannula use has been used
in stable COPD patients and compared to noninva-
sive ventilation.16 Both strategies reduce the resting
PaCO$_2$.

Patients on O$_2$ delivered by HFNC need frequent
and careful evaluation for progression of their respir-
atory failure and respiratory muscle fatigue. Koga
used a multivariable model to identify factors associ-
ated with HFNC failure.19 Failure was defined by the
need for intubation or to switch to NIV after HFNC use.
This model demonstrated that larger pleural effusions
and higher SOFA scores were associated with HFNC
failure. In a previous study, the lack of initial response
to HFNC, more severe disease, and additional organ
dysfunction are associated with increased risk of
HFNC failure.11 Lee reported that patients with he-
matologic malignancies and acute respiratory failure
would more likely require intubation if they had bacte-
Table 3 Physiologic studies and factors associated with HFNC failure

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>#</th>
<th>Type of pts</th>
<th>Location</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeong</td>
<td>Retrospective</td>
<td>173</td>
<td>ARF</td>
<td>ED</td>
<td>HFNC</td>
<td>NA</td>
<td>PCO₂ decreased in patients with PCO₂ &gt; 45</td>
</tr>
<tr>
<td>Bräunlich</td>
<td>Prospective, non-randomized crossover</td>
<td>11</td>
<td>COPD</td>
<td>Outpatient</td>
<td>HFNC 20 L/min</td>
<td>NIV</td>
<td>NFNC led to significant decreases in resting PCO₂. Between the devices we found no differences in pCO₂ levels.</td>
</tr>
<tr>
<td>Frat</td>
<td>Prospective, crossover</td>
<td>28</td>
<td>ARF</td>
<td>ICU</td>
<td>HFNC</td>
<td>NIV after HFNC</td>
<td>PO₂ increased more with NIV, HFNC tolerated better</td>
</tr>
<tr>
<td>Vargas</td>
<td>Prospective</td>
<td>12</td>
<td>ARF</td>
<td>ICU</td>
<td>HFNC at 60 L/min, esophageal pressure, breathing pattern, gas exchange, comfort, dyspnea were measured.</td>
<td>Non-re-breathing mask to keep O₂ Sat &gt;90%, CPAP at 5 cm H₂O</td>
<td>Compared to conventional O₂ therapy, HFNC improved inspiratory effort and oxygenation, CPAP increased PaO₂/FIO₂ more</td>
</tr>
<tr>
<td>Factors associated with HFNC failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koga</td>
<td>Retrospective</td>
<td>73</td>
<td>ARF</td>
<td>ICU</td>
<td>HFNC</td>
<td>NA</td>
<td>The extent of pleural effusion and the SOFA score were associated with HFNC failure</td>
</tr>
<tr>
<td>Lee</td>
<td>Retrospective</td>
<td>45</td>
<td>ARF¹</td>
<td>ICU</td>
<td>HFNC</td>
<td>NA</td>
<td>Patients with bacterial pneumonia more likely to fail HFNC</td>
</tr>
<tr>
<td>Kang</td>
<td>Retrospective</td>
<td>175</td>
<td>ARF</td>
<td>ICU</td>
<td>HFNC</td>
<td>NA</td>
<td>Intubation &gt;48 hr after HFNC use and failure increased mortality</td>
</tr>
</tbody>
</table>

¹with hematologic malignancy, ARF- acute respiratory failure, ED- emergency department, HFNC- high flow nasal cannula oxygen, ICU- intensive care unit, NA- not applicable, NIV- noninvasive ventilation, SOFA- sequential organ failure assessment.

In summary, HFNC devices can provide humidified oxygen at high flow rates with high FiO₂s. This method of oxygen delivery appears to be more comfortable than using noninvasive ventilation, and it does improve oxygenation, reduce respiratory rates, and reduce the sense of dyspnea. This modality has been studied most in patients with acute hypoxic respiratory failure. The study reported by Frat et al provides good evidence that patients with moderate to severe respiratory failure (PaO₂/FIO₂ < 200) may benefit the most.¹ Patients on HFNC need careful monitoring and early recognition of predictors of treatment failure to avoid prolonged use with ultimate and delayed intubation and worse outcomes. The more complex the patient’s underlying medical...
problems are the more likely HFNC therapy to fail.  

Author Affiliations: David Sotello is a fellow in Infectious Disease at the Mayo Clinic, Jacksonville, FL. Hawa Edriss is a fellow in Pulmonary and Critical Care Medicine at Texas Tech University Health Sciences Center in Lubbock, TX. Kenneth Nugent is a faculty member in Pulmonary and Critical Care Medicine at TTUHSC.

Submitted: 3/21/2016
Accepted: 4/6/2016
Reviewers: Cynthia Jumper MD
Published electronically: 4/15/2016
Conflict of Interest Disclosures: None

REFERENCES